Reviewer 1

Thank you for your comments.

We have changed the title and the last part of the abstract.

"Extrahepatic cholangiocarcinoma: current status of endoscopic approach and additional therapies"

3. We added new references.

4. We added more precise informations regarding preoperative drainage .

In a European multicenter study, Gouma et al, have shown that the postoperative outcomes in patients with pCCAs who undergone surgery and preoperative biliary drainage were not improved. However, in patients who undergone en bloc right hepatectomy the rate of mortality was lower[32].

In dCCAs, preoperative bile duct drainage is not always necessary unless neoadjuvant chemotherapy is planned and might be associated with an increased risk of cholangitis and postoperative infectious complications[33].

Some centers prefer preoperative biliary decompression in order to decrease the total bilirubin level under 3 mg/dl, whereas others recommend resection in patients without biliary drainage. In our center the decision to perform preoperative biliary drainage is made in the setting of multidisciplinary team and it is not generally recommended unless a severe liver dysfunction is suspected.

There are different data regarding the benefits of preoperative biliary drainage in jaundiced patients with pCCAs without absolute indications for biliary drainage[30]. The most recently studies concluded that routine biliary drainage does not impart any advantage since does not improve the morbidity or mortality of patients with resected pCCAs[32,34,35]. A recent meta-analysis and a systematic review showed that preoperative biliary drainage have not change the incidence of postoperative complications, hospitalization time, R0 and survival rate. However, in jaundiced patients, preoperative biliary drainage have decreased the post-operative mortality [36].

For dCCAs an European multicenter study have not found any differences regarding mortality rate in patients with preoperative biliary drainage[37]. Moreover,

in a recent retrospective study, a preoperative endoscopic biliary drainage was associated with a decrease in the survival rate[38].
The risk of endoscopic plastic stents occlusion is up to 60% therefor there are several groups of experts which recommend the preoperative nasobiliary drainage.
Kawashima et al has compared preoperative nasobiliary drainage with endobiliary stenting drainage in 164 patients with pCCAs. They have found a longer stent patency and a lower risk of cholangitis in nasobiliary group than endobiliary stenting group[42].

Reviewer 2

Thank you very much for your comments.

We change the title. We have added new references.

We disscued in more detail the RFA and Bt techniques.

PDT

In a recent meta-analysis conduct by Lu Y et al[114], overall survival was significantly better in patients who received photodynamic therapy than those who did not. Among the 8 trials (642 subjects), 5 assessed the changes of serum bilirubin levels, and/or Karnofsky performance status, as other indications for improvement. The incidence of phototoxic reaction was 11.11%. The incidence for other events in photodynamic therapy and the stent-only group was 13.64% and 12.79%, respectively.

A new model, of a photosensitizer-embedded self-expanding metal stent (PDT-stent) which provides a photodynamic effect without a systemic injection has been developed. The treatment could be repeated due to the incorporation of the polymeric photosensitizer into the mesh of the stent. The stent maintained its photodynamic power for at least 8 weeks. This type of stent, after light exposure creates cytotoxic free radical such as singlet oxygen, in the surrounding tissue and induces destruction of tumoral cells on animal models[115].

Brachytherapy

The purpose of the brachytherapy (BT) is to deliver a high local dose of radiation to the tumoral tissue, while sparing healthy tissue around. It can be adapted for right and left hepatic duct, and also for common bile duct lesions. It plays a limited but specific role in the curative intent treatment, in selected cases of early disease, as well as in the postoperative for small residual tumoral tissue. The indications for brachytherapy are as radical or palliative treatment. As radical treatment option is recommended alone in small inoperable tumors or in combination with external beam radiation therapy (EBRT) and/or chemotherapy in advanced disease for unresectable tumors. As well, BT may be used as adjuvant treatment after non-radical excision, possibly combined with EBRT. The most common indication for BT occurs as palliative in unresectable Klatskin tumors. The purpose is to prevent locoregional disease progression and to facilitate the bile outflow. The major aim is to improve the quality of life and to increase the survival. The treatment decision is recommended to be made personalized, for each patient[116].

Extrahepatic localization of CCAs, the absence of metastases, increasing calendar year of treatment, and liver transplantation with postoperative radiation therapy were factors significantly associated with improved survival[118,119].

In a recent study[122] 122 patients with CCAs have been successfully treated with HDR brachytherapy using the nasobiliary technique. The brachytherapy was not completed in 3 patients because either the catheter migrated between the ERCP and the treatment (2 patients) or the HDR after loader was physically unable to extend the source wire into the treatment site (1 patient). These 3 patients benefit from an external beam boost instead of HDR brachytherapy. Intraluminal HDR brachytherapy with a nasobiliary catheter is a minimally invasive method for administering neoadjuvant radiotherapy.

Reviewer 3

Thank you for your comments.

We have discussed in more detail the specific clinical features of eCCA.

We have underlined that improving serum levels of bilirubin is also a prerequisite for oncologists to start with chemotherapy.

We have discussed about cholangioscopy and about molecular targeted therapy .

Peroral cholangioscopy (POC) allowing direct visualization of the biliary tract with targeted biopsy of suspicious lesions has shown to be a useful diagnostic procedure in the evaluation of biliary strictures(Figure 7). A recent study[89] showed that POC use for the assessment of intraductal spread in potentially resectable pCCAs can detect more accurate and change surgical management. In the future, preoperative staging of CCAs should combine radiological with endoscopic – POC evaluation, in order to optimize surgical results.

Another study[90] had the aim to compare the performance characteristics of single-operator cholangioscopy (SOC)-guided biopsies and transpapillary biopsies with standard sampling techniques for the detection of CCAs. It showed that SOC-guided and transpapillary biopsies improve sensitivity for the detection of CCAs in combination with other ERCP-based techniques compared to brush cytology alone. However, it seems that these modalities do not significantly improve the sensitivity for the detection of malignancy in primary sclerosing cholangitis (PSC).

A very recent publication[91] evaluated a new developed POC classification system by comparing classified lesions with histological and genetic findings. Thirty biopsies were analyzed from 11 patients with biliary tract cancer (BTC) who underwent POC. An original classification of POC findings was made based on the biliary surface's form (F factor, 4 grades) and vessel structure (V factor, 3 grades). Histological malignancy rate increased with increasing F- and V-factor scores. The system was validated by comparing it to the histological diagnosis and genetic mutation analysis in simultaneous biopsied specimens. F-V classification is the first reported system to quantify and classify BTC based on POC findings.

Recent molecular studies have increased the understanding of the pathogenetic mechanism of CCAs, but to date, the clinical data on immune-directed therapies in CCAs are limited.

Inhibitors of isocitrate dehydrogenase (IDH) 1, IDH2 and pan-IDH1-IDH2 are currently being tested but in patients with iCCAs. Ivosidenib (IDH1 inhibitor) was tested in 73 patients with IDH1- mutant advanced CCAs in a phase I study, with no major adverse events reported[133]. A recent preliminary phase III trial showed a benefit for ivosidenib over placebo in terms of progression free-survival. One hundred eighty five patients with IDH1 mutant CCAs were randomly assigned to ivosidenib or placebo. This study has highlighted the importance of molecular profiling in CCAs[134] .

There are known some phase II studies with encouraging preliminary data for fibroblast growth factor receptors (FGFRs) inhibitors in patients with CCAs. Some FGFR inhibitors are currently being evaluated as first-line treatment, for example the FIGHT-302 study (NCT03656536) and the PROOF study (NCT03773302)[135-137].

Reviewer 4

Thank you for your comments.

We have up-dated the references.
In Fig. 6A, patient's name was deleted.